

mides are highly recommended. The alleviation of pain by morphine is often necessary and morphine can be readily used, as this form of shock is often late and after the secretion of the kidneys has been established.

OPSONIC INDEX AND VACCINE THERAPY.

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For many years scientists have been trying to explain the phenomena of immunity. Pasteur ascribed the death of the germs in the body to the exhaustion of suitable food. Others thought that the germs secreted products which gradually produced their own destruction. The theories which have enjoyed the longest life are those generally known as the cellular and the humoral, and their advocates have been divided into two schools. According to Metschnikoff and his followers, certain movable body-cells prevented or inhibited microbic invasion. On the other hand, Pfeiffer, Buchner, Bordet and particularly Erlich, have contended that the germs do not prosper in the system, owing to the antagonistic action of substances in the body-fluids. More recently Buchner has admitted that part of these substances undoubtedly have their origin in the polymorpho-nuclear leukocytes, thus seemingly abandoning the purely humoral theory. Metschnikoff, however, maintains that the substances actively concerned in the destruction of infecting bacteria, never act outside of the leukocytes. Neither theory has satisfactorily explained all questions. If, as Erlich assumes, immune substances are produced by those cells upon which bacteria exert their nefarious action, how may one interpret the natural immunity towards the many harmless saprophytes? And if Metschnikoff is correct, why do not phagocytes attack all bacteria? If we admit that active immunity has educated the cells to withstand certain bacteria, why is it that if in passive immunity the cells are stimulated, this immunity is exhibited only towards certain micro-organisms?

The work of Denys and Leclef,¹ Leishman,² Wright,³ and Douglas⁴ has resulted in the elaboration of a new theory, a theory which takes a stand really midway between those of the cellular and the humoral schools. This theory admits the fact that the remarkable activity of the leukocytes is a great factor in defending the system, but it maintains that the leukocytes are powerless to destroy the bacteria unless these have been previously influenced or prepared by the action of certain substances in the serum. These substances were given the name of "opsonins" by Wright, and he particularly emphasized the importance of estimating their amount in individual cases for diagnostic and therapeutic purposes.

The object of this paper is to call attention to the results obtained by the use of bacterial vaccines, generally speaking, and to show why the technic of determining the opsonic index was destined, in its present form, to meet with disfavor.

In order to disillusionize any who may think that Wright has given us an unassailable theory as to the causation of immunity, the following facts, as yet unexplained, are simply mentioned.

a. The bacteria of the same group as the bacillus of diphtheria are taken up by the leukocytes as well with heated serum as with normal serum. The question arises as to whether this is due to spontaneous phagocytosis in the absence of opsonins, or whether it is due to the presence of a thermostable opsonin (all others are thermolabile).

b. Many experiments with corpuscles obtained from various animals have shown that very infectious strains of germs are frequently more easily taken up by the phagocytes than less virulent cultures. This would seem to place our capillary tube experiments in contradiction with animal tests. For it has been similarly shown that a normal serum markedly bactericidal for anthrax, is by no means an indication of an animal's corresponding resistance to the disease.

For the *determination of opsonic indices* of patients, we require (1) normal sera for controls and the sera of patients, (2) washed corpuscles, (3) bacterial emulsion.

To obtain these various sera it is best to use the curved glass tubes devised by Wright. By wrapping a piece of bandage around the finger, a venous congestion is produced. One end of the closed glass tube, drawn out to a point, is used to stick the finger near the root of the nail. Both ends are broken off and blood is drawn up through the short limb, the lumen of which must not be too narrow. The straight end is again sealed with the flame, at a distance of 4 to 5 cms. from the body of the tube, so as to avoid heating the blood. The rarefied air now contracts and the blood is drawn further in, leaving the other end a bit free, so that it, too, can be sealed, though this is not necessary if it is to be used immediately. (One must always use freshly obtained sera in this work, as the opsonic power is gradually lost on standing, and this loss varies with different sera.) The blood is allowed to clot, and the tube suspended by its bent limb into the tube of a centrifuge and centrifuged. The serum being thus obtained, the bent limb is snapped off.

(2) A few drops of blood are received into a small glass tube two-thirds filled with 1.5% solution of sodium citrate. This solution disintegrates rapidly, so that it is best to make fresh solutions daily. The blood is well mixed and the tube centrifuged until the corpuscles settle. The clear fluid is pipetted off, and the corpuscles mixed with enough 0.85% salt solution to fill the tube as before. After again centrifuging and removing the supernatant fluid, the corpuscles are mixed, and are now ready for use. No attempt is made to preserve the thin gray upper film, rich in leukocytes, this having been found useless and time consuming. These corpuscles can be obtained from any person, provided that they are not subject to agglutination with other sera; it is more satisfactory to have the

worker furnish his own, and as they do not preserve their integrity after several hours' standing, this must be done daily. In making a series of counts, one must use the same tube of washed corpuscles throughout the series.

(3) The making of the emulsion varies with the organism used. For tubercle it is by far the easiest to use the dead, dry bacilli, such as may be obtained from Meister Lucius Brunning, Höchst, a. M. A small amount of this product is ground up in an agate mortar, first alone until finely powdered, then adding very slowly, drop by drop, 1.5% salt solution until first a paste and then an emulsion are made. Great care is required in all this to avoid, as far as possible, the presence of clumps. The emulsion is then sterilized (60° C. for 1 hour). It cannot be used for more than 10 days. It is kept in tubes with one end drawn out, so that the clumps which settle can be removed by cutting off this end, and the upper opalescent layers used. The emulsion should always be examined before use. If clumps are present, centrifuging is necessary. If not enough bacilli have remained in suspension, a new emulsion should be made. For making emulsions of other bacteria, a platinum-loopful of the growth from a live agar culture is diluted with 0.85% salt solution, and mixed thoroughly.

One volume of washed corpuscles, one of serum and one of bacterial emulsion are drawn up into a pipette and then blown out and thoroughly mixed on a clean slide, then drawn up into the pipette again and the end sealed in the flame. This must be done carefully but rapidly so as to exclude all possibility of spontaneous phagocytosis. The mixture is then placed in an incubator at a temperature of 37.5° C. For this work Dr. Freeman has devised an incubator with 20 tubes into which can be placed the glass pipettes. This instrument has been called an opsonizer.

After a definite time—20-30 minutes—the pipette is removed from the opsonizer, the end cut off and the contents used for examination. A drop is received upon one end of a slide, previously roughened by vigorous rubbing with emery paper, and the smear made by means of a so-called spreader. This is a slide, so broken as to give a barely visible concave edge. The white blood corpuscles adhere to the spreader until the end, and thus a film is obtained with almost all the W. B. C. at the very edge. Smears are fixed in corrosive sublimate solution. Tubercle is stained according to the Ziehl Neelsen method, other bacteria with carbol-thionin or methylene-blue.

The average number of bacteria ingested by one W. B. C. is the phagocytic index:—P. I. All polynuclear cells must be included in the count, excluding, however, those which have ingested obvious clumps of bacteria, and avoiding those parts of the slide where the cells are broken up, or where cells or bacteria are poorly stained. The patient's P. I. divided by the normal P. I. (the average of at least three tests with different healthy sera) gives the opsonic index:—O. I. For example:

Average normal: 100 W. B. C. contain 375 bacteria. P. I., 3.75.

Patient's serum: 100 W. B. C. contains 225 bacteria. P. I. 2.25.

And 2.25 divided by 3.75 equals 0.6, the O. I.

It is useless to count less than 100 cells, and while some claim that basing a result on less than 1,000²¹ cells is an error, the writer's experience has shown him that following the above rules in counting, different workers will obtain fairly constant results with the same slide. The entire technic must be accurately carried out. Improperly washed or aged corpuscles, inconstancy of temperature or period of incubation, varying density of emulsion, the use of pipettes of varying caliber, etc., so influence results as to make them valueless.

Instead of the methods which have been recommended to standardize the emulsions used, e. g., comparison with chemical suspension, counting the bacteria to the cubic millimeter, etc., it has been found⁵ that the making of a preliminary index determination with the normal serum as a control, is easier to carry out. Working with bacteria other than tubercle, the culture used should always be of the same age, to obtain, as near as possible, uniformity as regards their virulence.

Another possible source of error may be eliminated if the same volume of corpuscles is used for each test. This might occur if blood were used from the patient, instead of washed corpuscles and serum. The latter has been lately advocated⁶ with the idea of shortening the technic, but it seems as if it would also increase its accuracy.

The vaccines, with the exception of the tubercle, are nothing more than sterilized and standardized emulsions of cultures of the particular germ producing the infection. The organism is grown, e. g., in the case of staphylococcus, upon a broad slant agar surface, in the case of gonococcus upon ascitic agar; the 24 to 36 hours' growth is removed with 0.85% salt solution by means of a glass rod, and thoroughly emulsified by shaking in a test-tube for at least one-half hour to break up all clumps. The number of germs in the vaccine is calculated by comparing the number of germs and red corpuscles in a mixture of one part emulsion, one of freshly drawn blood, and any amount of salt solution as diluent. For this purpose one uses the same style of pipette as before, and a drop of the mixture is received on a slide and stained with any ordinary stain.

The vaccine should be kept in a dark bottle, $\frac{1}{4}$ of 1% lysol added to it to insure its keeping, and a rubber cap coated with paraffin, is used for a stopper. Instead of the cap used by Wright, a good rubber nipple can be advantageously employed. When an injection is to be made, the cap is sterilized with pure lysol and the needle stuck through it and sufficient vaccine drawn up into the syringe.

Tubercle vaccine is the "New Tuberculin Koch," though Wright has also used a bacillary emulsion made on the above principle. It appears, however, that excellent results are to be obtained with Koch's Old Tuberculin, Beraneck's, Denys' or Spengler's

Tuberculin, provided that the preparation employed be properly administered.

It must be remembered that Pasteur, Haffkine and others used vaccines to produce immunity long before Wright, but it is Wright who deserves the credit of having popularized their use.

I shall use Wright's own words in explaining the theories embodied in vaccine therapy.

"Protective substances may be defined as substances which enter into destructive chemical combination with bacteria, or, as the case may be, with other foreign elements introduced into the organism. A vaccine is any chemical substance, which, when introduced into the organism causes there an elaboration of protective substances. The bacterial vaccine inoculated, by entering into combination with the protective substances in the organism, withdraws a certain quantum from the organism. Under the stimulus of this deprivation, the cells of the organism are stimulated to activity, with the result that the protective substances withdrawn are replaced with usury.

"This is confirmed by the estimation of the opsonic index following inoculation of a vaccine. A diminution in protective substances is shown by a period of lowered index—the negative phase; this is followed by an increase of protective substances, the opsonic index is raised—this is the positive phase.

"When only a small dose of vaccine is inoculated, the negative phase may be so fugitive as hardly to appear on the record, but the positive phase will be correspondingly diminished. When an unduly large dose of vaccine is inoculated, the negative phase is prolonged and much accentuated. The positive phase may in such case make default.

"This shows that we can select the appropriate time and dose with certainty only by examining the blood and measuring its content in protective substances in each case before re-inoculating.

"For according as we choose our time and our dose, wisely or unwisely, we may obtain a cumulative effect in the direction of a positive phase or a cumulative effect in the direction of a negative phase."

If this were literally true, it is obvious that nothing could replace the *laboratory control of vaccine therapy*. Let us see whether this be so or not.

In a study of this subject⁵ in regards to tuberculosis, the writer found that the normal index varied within fairly narrow limits from day to day. In tubercular patients, with the lesions located elsewhere than in the lungs, the index was usually constantly low. Pulmonary cases showed indices which fluctuated considerably, being now low, then high, according as the patients were subject to auto-inoculations, i. e., discharges of bacterial products from the seat of their infection into their general circulation. Unless the occurrence of auto-inoculations be eliminated, one cannot in these cases estimate the effect of tuberculin injections, nor even expect benefit therefrom, for cumulative negative cannot be prevented.

Auto-inoculations are eliminated, or their frequency decreased, by a period of rest in bed. After a time it is found that a patient can be allowed moderate exercise without harm. In fact it has been recently shown⁷ that exercise can be so graduated, if controlled by the opsonic index, as to produce a series of auto-inoculations, with the intention of replacing the therapeutic use of tuberculin. If this could be generally done, it would be a great step in advance, for we would be inoculating our patient with tuberculin produced by his own particular species of bacilli, and this would do away with discussions as to whether in each individual case, bovine or human tubercular products should be used.

On the other hand, excellent results are being reported in cases of tuberculosis of glands, bones and skin.^{8,9} In the latter, owing to the poor vascularity of the tissues involved, injections alone cannot be relied upon to do much good. In fact, vaccine treatment is not meant to replace, but to assist other methods of treatment. Practically every European clinician of note is now, with great satisfaction, using tuberculin, without the index control, in selected cases of pulmonary, peritoneal, osseous and urogenital tuberculosis.¹⁰ In this country, the method is gaining advocates every day.¹¹ It is worthy of mention, that whereas patients have not only been greatly improved, but their tolerance for tuberculin raised a thousandfold, the writer has never seen or heard of an index being raised very high by treatment.

Staphylococcus infections have been most amenable to treatment with vaccines. Acne, furunculosis, sycosis, carbuncles, discharging sinuses, pyorrhea alveolaris, have all either yielded or improved so rapidly as to convince even skeptics of their efficiency. The writer has seen a case of sycosis and one of axillary abscesses complicated by a severe dermatitis, which had resisted all other therapy, clear up in about a week after the use of vaccines was begun. A case of lupus of the hand, complicated by pulmonary tuberculosis, with sputum rich in tubercle bacilli and staphylococci, and with a markedly intermittent temperature, was treated with tuberculin and occasional injections of staphylococcic vaccine for about three months. The patient remained at his work, he gained in weight, the sputum contained but few bacilli, the temperature fluctuated but slightly, and the lupus was arrested. Unfortunately at about this time business cares obliged the patient to work night and day, and he dropped the treatment until he had brought on a pulmonary hemorrhage which almost proved fatal. Rest in bed and another series of injections has again produced an arrest of the process in the lung, his temperature is normal and the lupus is almost healed. Another patient with cervical glands which had been operated, who presented several enlarged tubercular glands and discharging sinuses, and with slight pulmonary involvement, has been much improved by tuberculin and staphylococcic vaccine injections, there being but a very small spot on his neck which has not yet healed. Cases of staphylococcic sepsis²³ have been cured by vaccines

obtained by blood cultures from the patient. The writer tried this treatment on a little girl with a very severe endocarditis, but her condition was hopeless from the start, and, as expected, no benefit was obtained.

Streptococcic infections have not been as amenable to results as staphylococcic ones. Post-operative fistulas¹² have in some instances yielded to this form of treatment, while cases of erysipelas¹³ have not shown, on the whole, any more favorable course than non-injected ones. Septicemias²⁵ have in some cases been reported as cured by vaccines. Some cases of apparently fatal puerperal septicemias²² have been reported as cured by means of vaccines.

By the use of a typhoid serum, which is, according to Wright, really a bacterial vaccine, Chantemesse¹⁴ has had a mortality during the last six years of 4.3% of 1,000 cases, in contrast to 17% mortality of 5,621 cases in other Paris hospitals where no serum is employed. Wright has used typhoid vaccines as a preventive measure in the English army, first introducing them in 1897. After a while his method brought forth considerable discussion, and it was abandoned. Over a year ago a commission was appointed to investigate the matter, and resulted in vaccinations being reintroduced in the army.

Coli infections of the gall-bladder, urinary bladder, uterus and peritoneal cavity have been successfully treated with vaccines.²⁶

Cases of pneumonia, grippe, empyema and malignant endocarditis with sepsis are also reported, the latter treated without opsonic control.¹⁵ Investigations on coli and pneumococci have shown conclusively that these micro-organisms vary in each host, and that probably there are many species which exhibit the same microscopical and cultural appearances. This emphasizes the importance of using vaccines made from bacteria obtained from the patient. Wainstein²⁷ reports three cases of post-operative fistulas, ten cases of catharrhal endocervicitis, all of which cases had resisted other treatment, cured by pneumococcic vaccines.

Gonococcal infections have certainly been benefited by vaccines. Cole¹⁶ of Johns Hopkins reports cases of arthritis treated with excellent results, though index determinations he deems too inaccurate to be of use. Butler and Long¹⁷ of Chicago have treated twelve cases of vulvo-vaginitis in children with gonococcal vaccines. In four the clinical evidences of the disease disappeared in from ten days to three weeks, and the gonococcus was not to be found in smears from wipings from the vaginal mucosa, taken at intervals of several days. In five others a cessation of discharge and disappearance of gonococci from smears was attained after several weeks of treatment. The last three, owing to probable reinfections, are not so conclusive as the other nine. By comparison with a series of twelve cases treated with local antiseptics, the writers conclude that the vaccine method appears to be far more efficient and scientifically more tenable than the local antiseptic method. Dr. Vail¹⁸ of Chicago reports a series of twenty-five cases of acute and

chronic urethritis treated with vaccines, and while no conclusions are drawn, it would seem as if the results were good proof of their efficacy.

Hutchings¹⁹ of Detroit has used vaccines in thirty-two cases, there being in this series, urethritis, arthritis, vaginitis, some cases complicated by orchitis, prostatitis, cystitis or endometritis. His results are very good, but he comes to the natural conclusion that better results are to be had when other treatment is combined with bacterial inoculation.

E. Irons²⁴ also reports good results, especially in the chronic forms of arthritis. Results certainly justify the more general trial of gonococcic vaccines, more especially in chronic cases, such as arthritis, where our usual medication is most frequently of no value.

Vaccines made from the micrococcus neoformans have been used by the London school in cases of cancer, where they claimed the above coccus as a secondary infection is often responsible for the bad odor and rapid breaking down of tissue. Doyen of Paris is inclined to go so far as to believe his coccus the germ of cancer and uses a vaccine analogous to Wright's with apparently remarkable results, though in a study of the subject from the latter's standpoint, he was unable to find a constant normal index, nor was he able to get typical opsonic reactions with his vaccine. Though everything seems against the M. N. being the cause of cancer, no culture has ever been obtained from a closed cancer (the mammary gland is not closed), the writer is forced to admit that he saw many of Doyen's cases which seemed remarkably benefited by the treatment. It must be said that Doyen does not confine himself to his vaccine, but combines its use with whatever other method offers any chance of aiding the patient, so that it may naturally be questioned whether the same results would have been obtained without the vaccine. But in a great number of inoperative cases, seemingly hopeless cases, confirmed by pathological methods, results are certainly being obtained that are far ahead of anything the writer has ever seen.

Of three cases of cancer treated by the vaccine method, in one, a squamous celled carcinoma of the superior maxilla, Dr. Hutchings of Detroit²⁰ was able to prolong the patient's life several months as well as to make her much more comfortable. The other two cases, one of which was a carcinoma of the lung with lung metastasis, the second, generalized carcinomatosis from a uterine cancer, showed no benefit.

CONCLUSIONS.

1. Wright's researches have greatly advanced the study of immunity. Opsonins are apparently different from all the other anti-bodies.

2. Leaving aside the question of accuracy of technic, the estimation of opsonic indices is too difficult and time consuming to be of practical use in therapy.

3. In many forms of tuberculosis, in acne, furunculosis, gonorrhoeal arthritis, vaccines are our most effective weapons; in other infections they frequently give us excellent results.

The question as to the value of the opsonic index in diagnosis has been purposely omitted from this discussion.

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CEMENTWORKER'S ITCH.

Translated by D. W. MONTGOMERY, M. D., San Francisco.

René Martial has just published an article in the *Revue Pratique des Maladies Cutanées* (*) that should be of interest to physicians in San Francisco. It appears that cement frequently acts very harshly on the skin causing an irritation of the hands, breast and face, and it is very necessary, because of the difference in treatment, to distinguish the eruption from scabies, which it is apt to resemble.

The use of cement has increased particularly in San Francisco since the fire, and we therefore may expect to run across this particular affection with growing frequency.

What is cement? Cement is a mixture of carbonate of lime, silicic acid, alumina and iron ground up together and exposed to heat. It contains from one to five per cent of sulphuric acid as sulphates, two to five per cent of magnesia, and from eight to ten per cent of alumina. According to its composition it will "set" in from two to fourteen hours. Many samples of cement, analyzed by Martial, contained from 0.80 to 1.20 per cent of caustic soda.

Varieties of Cement. Its harmfulness. As can be seen by the enumeration of its constituents, cement is chemically very active, and contains many substances irritating to the skin, as carbonate of lime, silica, magnesia and sulphates. The activity of these substances is still further increased because of the

water with which it has to be mixed. The water macerates the skin of the workman, and at the same time increases the chemical activity of the substances in the cement, causing them to bite more viciously into the integument. As a rule, the quicker a cement "sets" the more dangerous it is to work with. The hands of the workman, as being most exposed to the chemicals, suffer most severely, but with those who work on vaults and ceilings the face, especially the periorbicular region, is often affected. Moisture is a predisposing cause, and erosions or cuts of the hands for example are frequently starting points for the eruption.

Description. The elementary lesion of the eruption is a papule, very small at its commencement, scarcely larger than a small pin head, which soon grows to the size of the head of an ordinary pin. This eruption is very itchy and this itchiness, like that of scabies, increases with the heat of the bed. Through the itchiness and consequent scratching the papules grow rapidly larger and become excoriated, and covered with a thin, black crust. In acute cases there may be edema of the fingers, back of the hands and forearms. As in the true itch the eruption shows a predilection for the webs of the fingers, and tends to be grouped about the wrists, about the bend of the elbows, and even in the axillae. As the men often work with shirt thrown open, the eruption frequently appears over the breast.

Contrary to the true itch there are very few lesions of the palms or of the thenar eminences, and the eruption often appears on the face, where it never appears in the true itch. Of course there are no burrows as in scabies.

Complications. The above is a description of the primitive eruption, that, however, shortly alters its appearance. When the attack has lasted some time the lesions extend, and flatten out, larger papules appear that are vaguely polygonal, polished, red, and quadrillated, and that become confluent, in short lichenification appears; or the excoriated papules become confluent seap and become eczematous. Lichenified and eczematous patches are found side by side. On becoming eczematous the eruption may extend to other parts of the body, as in other professional eczemas. The itchiness becomes so lively that the patient is unable to sleep, and moistens his hands constantly in cold water. The affection is always graver in summer than in winter, and seems clearly to be intensified by the sweat. Finally the lesions can become infected and give rise to pyodermites, but this is quite rare.

Duration. The duration and the intensity of the eruption are variable. One patient was afflicted for five months. Ordinarily on ceasing work the eruption clears up in one or two weeks.

Diagnosis. The diagnosis is easy if one thinks to inquire into the patient's occupation. The mimicry with scabies is, however, striking, and one must remember that a patient may have cement dermatitis and scabies at the same time.

Treatment. The treatment in the first place consists in stopping work and in the application for two to three days of Lassar's paste, which Martial advises to be made of equal parts of vaseline, lanoline, starch and oxide of zinc. The hands may first be soaked well in weak coal tar lotion, and then carefully dried before applying the paste, or five per cent of oil of cade may be added to the paste. Or tar glycerole may be used at first weak, afterwards stronger, applying it day and night, or tar glycerole may be applied at night and talc powder used during the day. If the eruption is acute with edema and leeting, hot compresses may be used or warm potato starch poultices; if there is infection boric acid compresses may be employed.

In some workshops thick gloves are furnished the men, and those that work on ceilings and vaults should wear large protecting spectacles.

* July, 1908.